

REMARKS

1. Status of the Claims

Claims 1-15 stand pending. Claims 1-11 stand rejected. Claims 12-15 stand withdrawn. Upon entry of the present amendment, claims 2 and 12-15 stand canceled. Applicants amend claim 1 to (1) more precisely recite the claimed subject matter, and (2) incorporate elements from previously presented claim 2. Applicants amend claim 3 to correct the dependency. Support for the amendment can be found at least, for example, from the originally presented claims, second full paragraph on pages 5, and second full paragraph on page 12 of the Specification. Accordingly, no prohibited new matter is introduced by entry of the present amendment.

Furthermore, the claims have been amended without prejudice to, or disclaimer of, the canceled subject matter. Applicants reserve the right to file a continuation or divisional application on any subject matter canceled by way of amendment.

Applicants thank the Examiner for providing the reference and resetting the time period to respond to the Office Action.

2. Finality of Restriction Requirement

Applicants note that the restriction has been made final. Applicants reserve the right to file a Petition on the Office's position regarding restriction in this matter.

3. Acknowledgement of Certified Priority Documents

Applicants note with appreciation the acknowledgement that the certified priority documents in the present application have been received.

4. Priority

Applicants note that the Office has asserted that the filing date of the claims is no earlier than PCT/JP2005/05786 (March 26, 2005), because no English language translation was

provided for the Japanese priority application, 2004-107512, filed March 31, 2004. Office Action at page 5.

Applicants attach hereto a verified English translation of JP Application 2004-107512, from which PCT/JP2005/05786 claims the priority. Applicants submit that with the translation they have perfected priority to the instant Japanese application and the filing date of March 31, 2004. *See* M.P.E.P. § 706.02(b).

5. Acknowledgement of Information Disclosure Statements

Applicants note with appreciation the acknowledgement of the Information Disclosure Statements filed September 29, 2006, May 24, 2007, and August 28, 2007.

6. Rejection of the Claims Under 35 U.S.C. § 103(a)

A finding of obviousness under 35 U.S.C. § 103 requires a determination of the scope and content of the prior art, the differences between the invention and the prior art, the level or ordinary skill in the art, and whether the differences are such that the claimed subject matter as a whole would have been obvious to one of ordinary skill in the art at the time the invention was made. *Graham v. John Deere Co.*, 383 U.S. 1, 148 U.S.P.Q. 459 (1966). These principles have recently been reaffirmed by the Supreme Court in *KSR Int'l Co. v. Teleflex Inc.*, 82 U.S.P.Q.2d 1385 (2007). Both the suggestion of the claimed invention and the expectation of success must be in the prior art, not in the disclosure of the claimed invention. *In re Dow Chem. Co.*, 837 F.2d 469, 5 U.S.P.Q.2d 1529 (Fed. Cir. 1988). Furthermore, one common inquiry in the above tests of obviousness is whether an ordinarily skilled in the art would have reasonable expectation of success to practice the claimed invention. *Examination Guidelines for Determining Obviousness under 35 U.S.C. 103 in View of the Supreme Court Decision in KSR International Co. v. Teleflex Inc.*, 72 Fed. Reg. 57,528 [*"Examination Guidelines"*].

Applicants respectfully traverse the following rejections to the extent they apply to the presently amended claims.

6.1. Rejection of Claims 1-4, 6-9, and 11

The Office rejects claims 1-4, 6-9, and 11 under 35 U.S.C. § 103(a) as allegedly being unpatentable over the following three references:

- 1) **Certik M. et al.**, *Desaturase-Defective Fungal Mutants: Useful Tools for the Regulation and Overproduction of Polyunsaturated Fatty Acids*, 16 TRENDS BIOTECHNOL. 500 (1998) [hereinafter "Certik"];
- 2) **Ueda R.**, *RNAi: A New Technology in the Post-Genomic Sequencing Era*, 15 J. NEUROGENETICS 193 (2001) [hereinafter "Ueda"]; and
- 3) **Mackenzie D.A. et al.**, *Isolation and Use of a Homologous Histone H4 Promoter and a Ribosomal DNA region in a Transformation Vector for the Oil-producing Fungus Mortierella alpina*, 66 APPL. ENVIRON. MICROBIOL. 4655 (2000) [hereinafter "Mackenzie"].

Certik allegedly teaches that desaturase-defective *Mortierella alpina* mutants are useful to produce polyunsaturated fatty acids (PUFAs). Office Action at pages 5-6. Ueda allegedly teaches RNAi as a means of selectively inhibiting expression of genes that are conserved across plants, animals, and fungi. Office Action at page 6. Mackenzie allegedly teaches means for delivering genetic material to achieve stable expression in *Mortierella*. *Id.* The Office asserts that a skilled artisan, in view of Certik, Ueda, and Mackenzie, would have been motivated to employ RNAi to inhibit the activity of *M. alpina* desaturases. Office Action at page 7.

Applicants respectfully traverse the rejection to the extent it applies to the amended claims. Claim 2 stands canceled upon entry of the present amendment, mooted the rejection. Claim 1 as amended recites a method of breeding lipid producing fungi by suppressing expression of a specific *Mortierella* gene with an RNAi method or a co-suppression method. None of the reference teaches or suggested a co-suppression method as presently recited. The rejection is thus improper, because the alleged prior art references fail to teach or suggest all claim elements. *See e.g., CFMT, Inc. v. Yieldup Int'l Corp.*, 349 F.3d 1333, 1342, 68 U.S.P.Q.2d 1940, 1947 (Fed. Cir. 2003).

Certik fails to teach affecting *Mortierella* genes with an RNAi method or a co-

suppression method, because it only teaches decreasing the desaturase activity by mutating the gene or using specific enzyme inhibitors. Mackenzie only teaches, at best, that *M. alpina* was successfully transformed with “a” genetic material. It does not otherwise overcome the defects of Certik. Ueda is asserted for allegedly teaching that “RNAi provided a means of selectively inhibiting expression of genes of choice that was conserved across a wide variety of organisms including plants animals and fungi.” Office Action at page 6. However, it was simply not known at the priority date of the application whether the RNAi approach would work in *Mortierella* in order to try to influence the production of lipids, and in particular, PUFAs. The combination of the references provides no expectation that the putative combination would successfully work. Applicants even generally discuss the unpredictability of the RNAi method:

Further, while the gene expression repressing effects of the RNAi method have been well-documented in many organisms for example, ***whether or not the method will be effective in a specific organism cannot be known until the method is actually carried out.*** For example, there has been no report that suggests the effectiveness of the RNAi method in lipid producing *Mortierella*.

See Specification, paragraph bridging pages 6-7 (emphasis added). Ueda’s allegedly teaching, as well as the teachings of the other two references, fail to provide an expectation of success let alone the outcome achieved. Hence, Ueda does not overcome the defects of Certik as discussed above. The Office appears to use improper hindsight through the teaching of the present Specification to pick and choose from the various elements to achieve the asserted combination.

Furthermore, Applicants show that it is possible using the RNAi method to control the degree of suppression. Applicants direct the Office to Example B of the Specification, which describes the construction of two RNAi suppression constructs and characterization of corresponding transformants. Specification at pages 36-44. One construct, pDura5Mei51, allows the expression of a double stranded RNA corresponding to about 700 bp of the MAELO gene, while another construct, pDura5Mei41, allows the expression of a double stranded RNA corresponding to about 500 bp of the MAELO gene. *Id.* at 40. Strains transformed with pDura5Mei51 showed a complete suppression of the synthesis of very long-chain saturated fatty acids, while the synthesis was only partially suppressed in strains transformed with

pDura5Mei41. *See* Specification, Table 2 on page 43. These data indicate that it is possible to fine-tune the degree of suppression of *M. alpina* desaturases with an RNAi method. Certik discloses certain randomly produced *M. alpina* mutants that are rendered **completely defective** in certain enzymes of the lipid synthesis. *See* paragraph under the heading “Fatty-acid-desaturase-defective mutants of *M. alpina*” on page 501. Similarly, Ueda describes RNAi “a powerful tool for **knocking out** the activity of specific genes.” *See* first paragraph on page 201 (emphasis added). The observed advantage of the present application, for example controlled suppression, amounts to **an unexpected result**, because all references teach is an on-off switch result, and not fine-tuned or controllable regulation. Accordingly, the presently recited methods are non-obvious in view of the alleged prior art references.

Overall, the Office improperly rejects the claims in view of Certik, Ueda, and Mackenzie. Accordingly, Applicants respectfully request withdrawal of the rejection and allowance of claims 1, 3-4, 6-9, and 11.

6.2. Rejection of Claim 1

The Office rejects claim 1 under 35 U.S.C. § 103(a) as allegedly being unpatentable over **Takeno S. et al.**, *Establishment of an Overall Transformation System for an Oil-Producing Filamentous Fungus*, *Mortierella alpina* 1S-4, 65 APPL. MICROBIOL. BIOTECHNOL. 419 (2004) [hereinafter “Takeno”]. Specifically, Takeno allegedly discloses the establishment of stable transfectants of *M. alpina* using a microprojectile bombardment-based transfection system. Office Action at page 7. The Office asserts that a skilled artisan at the time of the invention would have used the method of Takeno to suppress the expression of a PUFA biosynthetic gene. *Id.*

Applicants traverse the rejection to the extent it applies to the amended claim 1. The Office explicitly states that Takeno is available as prior art because the foreign priority filing date has not been perfected for the present application. Applicants have perfected priority to the instant Japanese application and the filing date of March 31, 2004. *See* Section 4. As the perfected filing date antedates the on-line publication date of Takeno, May 12, 2004, Takeno is

no longer available as a prior art reference. The Office's rejection relying on Takeno is thus moot. Applicants respectfully request withdrawal of the rejection and allowance of claim 1.

6.3. Rejection of Claims 2-8

The Office rejects claims 2-8 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Takeno as applied to claim 1 and further in view of Ueda and Mackenzie. The Office admits that the primary reference Takeno does not teach the use of RNAi to affect the expression of a PUFA biosynthetic gene. Office Action at page 8. The Office apparently uses secondary references Ueda and Mackenzie to cure the defect.

Applicants disagree and traverse. The Office is reminded that the primary reference Takeno is no longer available as prior art given the submission of the verified English language translation of the Japanese priority application, filed March 31, 2004. *See* Sections 4. and 6.2. Ueda and Mackenzie, alone or combined, fail to teach the instant claims, because neither teaches an RNAi method or a co-suppression method to suppress gene expression in *Mortierella*. *See* Section 6.1. As the references cannot be combined to form a *prima facie* obviousness rejection, it should be withdrawn. Additionally, claim 2 stands canceled upon entry of the present amendment, mooting the rejection. Accordingly, Applicants respectfully request withdrawal of the rejection and allowance of claims 3-8.

6.4. Rejection of Claim 5

The Office rejects claim 5 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Certik, Ueda, and Mackenzie as applied to claims 1-4, 6-9, and 11, and further in view of **White** T.C. *et al.*, U.S. Patent No. 6,939,704 [hereinafter "White"]. White allegedly teaches that filamentous fungi could be transfected by calcium chloride treatment, electroporation, or particle bombardment. Office Action at page 10. The Office admits that the combination of Certik, Ueda, and Mackenzie fails to teach gene delivery by electroporation or particle bombardment. *Id.* The Office apparently applies White to cure this defect.

Applicants disagree and traverse. First, the Office improperly combines Certik, Ueda, and Mackenzie, because a skilled artisan would **not** have had a reasonable expectation of success to combine the Certik, Ueda, and Mackenzie. *See* Section 6.1. It is the present application that **first** discloses the successful employment of the RNAi method to influence lipid synthesis, *e.g.*, PUFA biosynthesis, in *Mortierella*. *Id.* Additionally, the present application shows that the use of RNAi in affecting *M. alpine* desaturases offers at least one unexpected advantage—ability to fine-tune the degree of suppression. *Id.* The Office thus appears to use improper hindsight through the teaching of the present Specification to achieve the asserted combination. Second, White only teaches, at best, various methods to transfect filamentous fungi. It does not otherwise overcome the defects of Certik, Ueda, and Mackenzie as discussed in Section 6.1 *supra*. As the combined references fail to form a *prima facie* obviousness rejection, the rejection should be withdrawn, and claim 5 allowed.

6.5. Rejection of Claims 9-10

The Office rejects claims 9 and 10 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Certik, Ueda, and Mackenzie as applied to claims 1-4, 6-9, and 11, and further in view of **Parker-Barnes** J.M. *et al.*, *Identification and Characterization of an Enzyme Involved in the Elongation of n-6 and n-3 Polyunsaturated Fatty Acids*, 97 PROC. NAT. ACAD. SCI. USA 8248 (2000) [hereinafter “Parker-Barnes”]. Parker-Barnes allegedly teaches a gene encoding a fatty acid elongase from *M. alpina*. Office Action at page 11. The Office alleges that a skilled artisan, in view of Certik, Ueda, and Mackenzie, would have been motivated to utilize the RNAi method to suppress the elongase gene disclosed in Parker-Barnes. *Id.*

Applicants disagree and traverse. First, the Office improperly combines Certik, Ueda, and Mackenzie, because a skilled artisan would **not** have had a reasonable expectation of success to combine the Certik, Ueda, and Mackenzie. *See* Section 6.1. It is the present application that first discloses the successful employment of the RNAi method to influence lipid synthesis, *e.g.*, PUFA biosynthesis, in *Mortierella*. *Id.* Additionally, the present application shows that the use of RNAi in affecting *M. alpina* desaturases offers the unexpected advantage—ability to fine-tune

the degree of suppression. *Id.* The Office thus appears to use improper hindsight through the teaching of the present Specification to achieve the asserted combination. Furthermore, Parker-Barnes only teaches, at best, an *M. alpina* elongase gene. It does not otherwise overcome the defects of Certik, Ueda, and Mackenzie as discussed in Section 6.1 *supra*. As the combined references fail to form a *prima facie* obviousness rejection, it should be withdrawn, and claims 9-10 allowed.

CONCLUSION

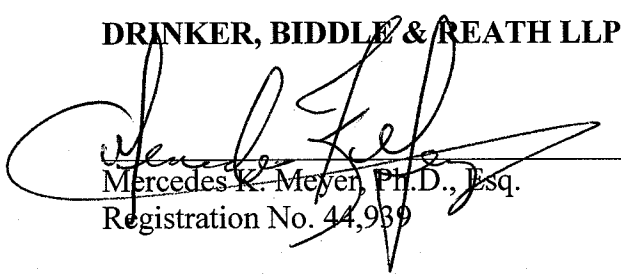
Should the Examiner have any questions or comments regarding Applicants' amendments or response, please contact Applicants' undersigned representative at (202) 842-8821. Furthermore, please direct all correspondence to the below-listed address.

In the event that the Office believes that there are fees outstanding in the above-referenced matter and for purposes of maintaining pendency of the application, the Office is authorized to charge the outstanding fees to Deposit Account No. 50-0573. The Office is likewise authorized to credit any overpayment to the same Deposit Account Number.

Respectfully submitted,

DRINKER, BIDDLE & REATH LLP

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Mercedes K. Meyer, Ph.D., Esq.
Registration No. 44,939

CUSTOMER NO. 55694
DRINKER, BIDDLE & REATH LLP
1500 K Street, N.W., Suite 1100
Washington, D.C. 20005-1209
Tel: (202) 842-8800; Fax: (202) 842-8465